Energy metabolism in amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is characterised by the progressive degeneration of upper and lower motor neurons. Besides motor neuron degeneration, ALS is associated with several defects in energy metabolism, including weight loss, hypermetabolism, and hyperlipidaemia. Most of these abnormalities correlate with duration of survival, and available clinical evidence supports a negative contribution of defective energy metabolism to the overall pathogenic process. Findings from animal models of ALS support this view and provide insights into the underlying mechanisms. Altogether, these results have clinical consequences for the management of defective energy metabolism in patients with ALS and pave the way for future therapeutic interventions.

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Introduction

Amyotrophic lateral sclerosis (ALS) is characterised by the simultaneous degeneration of lower (spinal and bulbar) and upper (corticospinal) motor neurons, leading to progressive muscle atrophy and paralysis.[1] Motor neuron degeneration is mostly associated with pathological aggregation of ubiquitin, the fused in sarcoma protein (FUS), and the TAR DNA binding protein of 43-kDa TDP-43 (TDP-43) in the cytoplasm of motor neuron cell bodies.[2,3] ALS generally leads to death within 2–3 years of diagnosis, mostly from respiratory failure.[4,5] The incidence of this disorder (1·5–3·0 per 100 000) is similar to that of multiple sclerosis, but the prevalence of ALS is much lower owing to the poor prognosis. Clinical presentation is heterogeneous, which suggests that ALS is a syndrome rather than one nosological entity.[5] In support of this theory, various seemingly unrelated causes of ALS have been described, including toxic[6,7] and genetic[8] causes. Most ALS cases (90%), however, are of unknown origin, with no obvious family history, and are termed sporadic ALS. No firmly replicated genetic risk factor for sporadic ALS has emerged from genome-wide association studies, except the association with a narrow region on chromosome 9p21.[9,10] ALS is sometimes associated with non-motor symptoms, most notably with frontotemporal dementia,[11] and the occurrence of TDP-43-positive aggregates in patients with ALS, frontotemporal dementia, or both, strongly supports the existence of a pathophysiological continuum between these two disorders.[12]

Initially, pathological abnormalities in ALS were thought to be restricted to motor neurons, but descriptions of a wider dissemination of effects throughout the body have challenged this classic paradigm. Several lines of investigation have clearly demonstrated that ALS is a systemic disease, including presentations of diffuse brain involvement. Further extending this notion, ALS disease seems to be restricted not only to the CNS but also affects whole-body physiology. In particular, energy metabolism is severely altered in patients with ALS, which has notable clinical implications. In this Review, we focus on the alterations of energy homoeostasis in ALS, how they contribute to the overall pathogenic process, and how they might constitute targets for new therapeutic strategies.

Impairment of energy metabolism

Energy homoeostasis results from the balance of energy intake and energy expenditure. In healthy people, food intake and nutrient absorption are theoretically in balance with basal (resting) and activity-induced energy expenditure (figure 1). This balance in healthy adults leads to roughly stable energy stores, mostly in the form of triglycerides in adipocytes, and hence to a stable body-mass index. Energy homoeostasis requires that uptake of nutrients in cells, including glucose and lipids, is adequately controlled by the glucose–insulin axis. Any perturbation in insulin signalling leads to decreased cellular uptake of nutrients in peripheral tissues and, therefore, increased energy stores, as seen, for instance, in type 2 diabetes mellitus. Another source of increased energy stores is the western lifestyle, which for many people is characterised by overeating, little physical activity, and high body-mass index. Obesity is linked to insulin resistance, which leads to decreased sensitivity of the peripheral tissues, such as skeletal muscles, to insulin and limits nutrient entry into these cells.

In ALS, energy balance is profoundly impaired owing to higher energy expenditure than intake (figure 1, table, panel). Patients with ALS are generally lean with a normal or low body-mass index[13–15] and typically lose weight and body fat as disease progresses;[15–18] therefore, energy stores are decreased. Several mechanisms contribute to energy imbalance in ALS. First, bulbar muscle weakness leads to dysphagia, and thus, to lowered food intake.[19] Second, resting energy expenditure is increased in patients with ALS. In human beings, energy expenditure is generally measured at rest by indirect calorimetry. Comparison of this value with a theoretically calculated energy expenditure, which is normally based on the Harris and Benedict equation, yields a metabolism ratio. If the ratio is higher than 1, the individual is deemed hypermetabolic. By use of this method, increased energy expenditure[20–22] has been demonstrated in patients with familial and sporadic ALS. Hypermetabolism in patients with ALS is a surprising finding, as denervation-linked muscle wasting would be assumed to lead to hypometabolism owing to the loss of a major site of nutrient consumption. Thus, the cause of this feature is currently unknown.

Hyperlipidaemia has been put forward as an explanation for energy imbalance in ALS. Some studies have

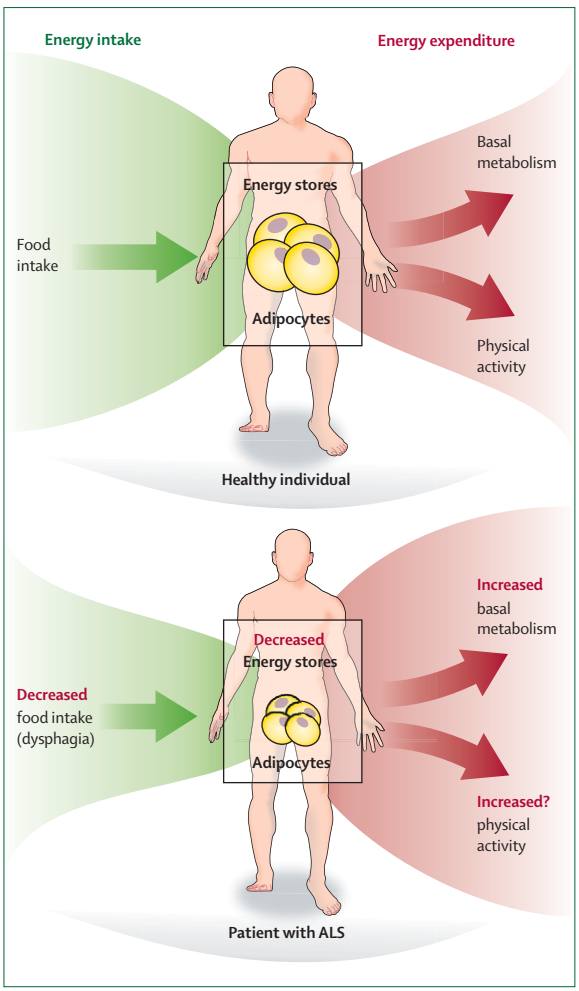

Figure 1: **Comparison of energy homoeostasis in healthy individuals with that in patients with ALS**

Food intake and energy expenditure by basal metabolism and physical activity are balanced in healthy individuals leading to roughly stable energy stores. In patients with ALS, energy storage is decreased, resulting from dysphagia, in the case of bulbar symptoms, and increased energy metabolism. Increased physical activity is also a potential contributor to energy imbalance. ALS=amyotrophic lateral sclerosis.

	Comment
Weight loss[13–18]	Weight loss occurs in a substantial proportion of patients with ALS and is associated with poor prognosis
Decreased food intake[19]	A result of dysphagia
Hypermetabolism[20–22]	Increased energy expenditure is reported compared with theoretical calculation of energy expenditure and has been repeatedly observed in sporadic and familial forms of ALS throughout disease progression
Hyperlipidaemia[23–27]	Hyperlipidaemia has been reported in two independent cohorts of patients with ALS from France and Germany, but not in a cohort from Italy
Glucose intolerance[28,29]	A substantial proportion of patients with ALS develop glucose intolerance
Muscle mitochondrial abnormalities[30–33]	Mitochondrial dysfunction is seen in skeletal muscle of patients with ALS as the disease develops, possibly owing to progressive denervation

ALS=amyotrophic lateral sclerosis.

Table: **Evidence related to abnormal energy metabolism in ALS**

demonstrated increased blood lipid concentrations. For instance, among 369 French patients with ALS, nearly two-thirds had increased LDL-cholesterol concentrations, decreased HDL-cholesterol concentrations, or both,[23] and 140 (38%) had abnormally high LDL-to-HDL ratios. Increased concentrations of circulating apolipoprotein E were also seen in the same cohort of patients[24] and in a German cohort.[25] Contrasting findings were, however, seen in a group of Italian patients.[26] An increased LDL-to-HDL ratio is frequently taken to be a surrogate marker of insulin resistance, and both have been reported in patients with ALS.[27,28]

The causes of hyperlipidaemia are unclear in patients with ALS. First, muscle mitochondrial defects might lead to hyperlipidaemia, but the nature of such defects is incompletely characterised.[29–32] Increased food intake could be another cause. Unfortunately, few prospective or case-control studies have been done to investigate the dietary habits and energy of people before they develop ALS,[33–35] unlike in Parkinson's disease,[36] owing to the high number of sporadic cases and highly variable age of onset (age 40–60 years). An important question to answer would be whether presymptomatic patients with ALS compensate for hypermetabolism with increased energy intake, thereby raising the risk of hyperlipidaemia and insulin resistance. In the absence of such studies, the cause and effect relation between ALS and energy metabolism remains difficult to establish.

Energy metabolism and prognosis

The occurrence of defective energy metabolism in patients with ALS is not necessarily pathogenic or related to disease status. Several correlative studies have, however, provided some indication of a pathogenic role. First, weight loss and malnutrition are negatively associated with survival and are important prognostic factors in ALS.[15,37–39] By contrast, hyperlipidaemia[23] and increased concentrations of circulating apolipoprotein E[24] are positively correlated with survival in ALS, which suggests that increased availability of lipids in blood is beneficial. Finally, ALS onset is later in patients with type 2 diabetes.[26,40]

No links between genetic risk factors and impaired energy metabolism—and therefore survival—in sporadic ALS have been established. An association between the *APOE* ε4 allele and bulbar onset of ALS was purported,[41] but subsequent larger studies found no evidence of effects of *APOE* genotypes on the site of onset or survival.[42,43] Other key metabolic genes, such as *PPARGC1A*, which encodes the transcriptional co-activator PGC1α, are modifier genes in other neurodegenerative diseases, such as Huntington's disease,[44] but studies of these as potential candidate genes for ALS are yet to be done (panel).

The role of environmental factors has probably been largely underestimated. For instance, in a study of 658 Italian patients with ALS and 658 matched healthy controls, blood lipid profiles were similar in the two

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groups, suggesting that patients with ALS were not especially susceptible to hyperlipidaemia, and hyperlipidaemia was not associated with increased survival in patients.[26] As these findings contrast with those from the French and German studies,[23,25] they might reflect an intrinsic heterogeneity in ALS disease presentation, but could also indicate an effect of environmental cues. For instance, differences in dietary habits between countries might have notable effects on ALS course.

Although hyperlipidaemia did not directly affect survival in the Italian study, some, albeit small, protective effects of hyperlipidaemia and increased LDL-to-HDL-cholesterol ratio were seen on respiratory function, which is viewed as the most important prognostic factor in ALS.[45] The association between decreased blood lipid concentrations and respiratory impairment might, therefore, indicate an indirect association between lipid values and survival. An urgently needed meta-analysis of findings is underway to clarify this important issue. Overall, the nutritional status of patients with ALS is widely accepted to be an important prognostic factor, but the extent and mechanisms of a protective effect deserve further investigation.

Panel: Potential causes of hypermetabolism in amyotrophic lateral sclerosis

Hypermetabolism is defined as raised oxygen consumption owing to increased mitochondrial metabolism

- The increase in metabolic rate has been attributed to uncontrolled fasciculations, increased work of respiratory muscles, or mitochondrial defects, but causal relationships remain speculative
- No links between genetic risk factors and impaired energy metabolism have been firmly established, although mutant human *SOD1* seems to cause energy deficit in transgenic mice
- *APOE* and *PPARGC1A* are other potential candidate metabolic genes, but data are unconfirmed or not yet available in amyotrophic lateral sclerosis
- Work in animal models indicates that increases in energy expenditure are intrinsically linked to the disease process, but as hypermetabolism largely precedes denervation in animal models, this feature is not caused by denervation
- Many environmental modifiers known to modulate disease course also affect metabolism; neurotoxins, exercise, response to hypoxia, and effects of statin therapy are areas of particular interest

Energy metabolism and motor neuron degeneration

As study of the presymptomatic and early phases of ALS is very difficult in people, animal models are crucial to research. Since the discovery of mutations in the *SOD1* gene linked to familial ALS,[8] several transgenic mouse and rat models overexpressing various mutant isoforms have been developed that produce good representations of the cardinal symptoms of ALS in human beings.[46] In transgenic mice expressing human mutant *SOD1*, upper and lower motor neurons degenerate,[47] and tremor, paralysis, and muscle atrophy develop that spread from the lower to the upper limbs. Dysphagia and bulbar symptoms are also seen.[48]

Metabolism is higher and bodyweight and fat mass are lower in mutant *SOD1* mice than in wild-type mice.[49] These signs occur weeks before disease onset.[49] Thus, muscle hypermetabolism and energy deficit are intrinsic to ALS pathogenesis. By contrast with findings in patients, mutant *SOD1* mice have decreased and not increased concentrations of lipids in blood.[50] The correction of energy deficit in mutant *SOD1* mice through feeding them a high-fat diet delayed disease onset, increased lifespan, reduced muscle denervation, and improved motor neuron survival.[49,51] Conversely, caloric restriction of mutant *SOD1* mice accelerated the overall disease course and hastened death.[52,53]

Findings from newly generated TDP-43 animal models also imply defective energy homoeostasis in ALS. Loss of TDP-43[54] or its overexpression[55,56] both led to growth retardation, and thus impaired energy homoeostasis. Furthermore, adult loss of TDP-43 led to massive decreases in adipose tissue, probably through muscle hypermetabolism,[54] and TDP-43 overexpression led to the formation of morphologically abnormal mitochondria.[55,56] TDP-43-ALS, like mutant *SOD1*-ALS, therefore, seems to be associated with impaired energy homoeostasis in transgenic animals. The mechanisms linking TDP-43 and mitochondrial physiology need further investigation.

Abnormalities in muscle energy metabolism have been suggested as the direct cause of energy deficit and hypermetabolism in mutant *SOD1* mice. Cellular levels of ATP are decreased[57,58] and expression of mitochondrial uncoupling proteins and concentrations of markers of lipid and carbohydrate use are increased.[49,59] Several reports have indicated the existence of mitochondrial defects in the muscle tissue of patients with ALS that develop as the disease progresses.[30–32] Low-level mitochondrial defects might, however, be present earlier, as increased sensitivity of ALS myoblasts to oxidative stress has been seen in some patients.[29] Localisation of mitochondrial defects to regions close to neuromuscular junctions has also been suggested.[60] The extent and origin of such mitochondrial dysfunction remain controversial, however, and the impairment of energy metabolism seen in patients with ALS and mutant *SOD1* mice might be due at least partly to dysfunctional regulation of metabolic pathways. This effect might be potentiated by the co-occurrence of a mitochondrial defect.

Decreases in the efficiency of muscle energy metabolism lead to motor neuron degeneration. Mice overexpressing the mitochondrial brown fat uncoupling protein 1 in muscles, as a model of muscle-restricted

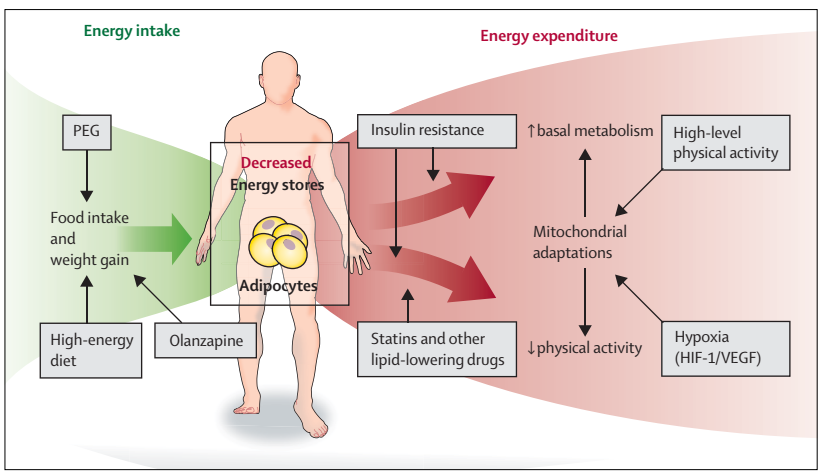

***Figure 2*: Modification of energy metabolism in amyotrophic lateral sclerosis**
Various nutritional therapies, such as PEG and change to a high-energy diet, might increase energy intake in patients with amyotrophic lateral sclerosis; olanzapine has been linked to weight gain in other disorders and is being investigated in amyotrophic lateral sclerosis.[95] The main risk with such interventions is insulin resistance, which could shut off nutrient supply to tissues. Use of statins or other lipid-lowering drugs might decrease insulin resistance, but can diminish energy stores. An abnormally high degree of physical activity or hypoxia might notably modify mitochondrial metabolism, and abnormalities in related pathways, such as mutations in the VEGF promoter, could lead to degeneration of motor neurons. PEG=percutaneous endoscopic gastrostomy. HIF=hypoxia-inducible factors. VEGF=vascular endothelial growth factor.

hypermetabolism, displayed age-dependent deterioration in neuromuscular junctions that correlated with progressive signs of denervation and mild, late-onset motor neuron pathology.[61]

Muscle hypermetabolism might be driven by expression of a mutant gene in skeletal muscle. In mutant *SOD1* mice, gene overexpression restricted to skeletal muscle was sufficient to induce severe muscle atrophy associated with significant reductions in muscle strength and ultrastructure[62] and denervation of the neuromuscular junction, paresis, and motor neuron degeneration.[63] Muscle hypermetabolism might also be indirectly triggered by mutant gene expression in non-muscle cell types, most notably macrophages and monocytes, which have been largely involved in the toxic effects of mutant *SOD1*.[64] Further experimental work is needed to delineate the exact contribution of each cell type to the pathobiochemistry of ALS-like pathology in mutant *SOD1* mice, but overall animal models of ALS have shown convincingly that energy metabolism impairment is an early event, intrinsic to the ALS disease process, and affects survival.

Modification of energy metabolism

Most, if not all, potential environmental modifiers known or postulated to modulate the ALS disease course affect energy metabolism. The four main potential areas of interest in ALS are neurotoxins, exercise, response to hypoxia, and statin treatment (panel). We discuss these features below in the context of ALS, but also in the context of other motor neuron diseases when relevant information is available.

Food-related neurotoxic effects

Neurolathyrism, which was already recognised by Hippocrates, is the most prominent example of a motor neuron disease induced by food. Excessive consumption of the legume *Lathyrus sativus* alone was thought to be sufficient to cause the typical upper motor neuron disease. Early descriptions indicated that the disease was identical to hereditary spastic paraparesis, but it was later shown to have subclinical effects in anterior horn cells lending further support to an analogy with ALS.[65] The toxic agent in *L sativus* is probably the excitatory aminoacid β-*N*-oxalylamino-L-alanine;[66] however, studies in well nourished primates have demonstrated only largely reversible deficits of the corticospinal tracts and to a minor degree of lower motor neurons.[67] Field studies in Bangladesh revealed that patients with neurolathyrism who subsisted almost exclusively on *L sativus* typically experienced onset of non-reversible disease during periods of starvation and during hard work in the cold.[68] These findings strongly suggest that metabolic changes associated with starvation, including lack of carbohydrates, increased mobilisation of insufficient lipid stores, and potentially metabolic acidosis, are necessary to trigger the development of a permanent motor neuron disease.[68]

The neurotoxic disease neurocassavaism also develops during periods of starvation after consumption of the bitter cassava *Manihot esculenta*.[69] Clinically, neurocassavaism is identical to neurolathyrism, being characterised by a classic spastic paraparesis.[68] The toxic agent of the bitter cassava is the cyanogenic glycoside linamarin, which is consumed if this food does not undergo the correct detoxification processes.[70] The metabolic consequences of consumption are even more obvious than those of neurolathyrism, and include inhibition of the mitochondrial chain, metabolic acidosis, an increased demand on carbohydrate and lipid stores, and so-called chemical hypoxia. Thus, neurolathyrism and neurocassavaism are two toxic motor neuron diseases whose onsets require a modification of energy metabolism, notably through starvation. We suggest that a similar pathogenic role of energy metabolism could be at work in ALS.

Exercise and abnormal response to hypoxia

Exercise and abnormal response to hypoxia, two largely postulated risk factors for ALS, are potent modifiers of muscle energy metabolism. The epidemiological association between ALS and physical activity remains controversial,[71] as conflicting results have been seen in case-control studies. These differences might be due to multiples biases. For instance, increased incidence of ALS has been reported in Italian soccer players,[72] but other environmental confounders might be relevant, such as exposure to pesticides. Nevertheless, the experimental evidence supporting exercise as a modulator of ALS course is ample. First, exercise modulates muscle mitochondrial function by promoting biogenesis.[73] Different types of exercise have different effects on muscle

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energy metabolism; for instance, endurance running promotes oxidative metabolism and swimming promotes glycolysis. In mutant *SOD1* mice, exercise seems differentially protective against pathology dependent on the type of exercise. Moderate exercise and swimming[74] seem to protect the neuromuscular system of mutant *SOD1* mice more efficiently than exhaustive running training.[75] Overall, exercise is likely to be protective (figure 2); the molecular pathways underlying such protection remain to be investigated.

Abnormal response to hypoxia is involved in ALS and seems to be one of the most potent modifiers of energy metabolism (figure 2), although whether the contribution is direct or indirect, or both, needs further investigation. In mice, abrogation of the hypoxia responsive element in the VEGF promoter (VEGFδ/δ mice) leads to motor neuron degeneration with numerous typical features of ALS.[76] Conversely, administration of VEGF to mutant *SOD1* mice or rats improved survival.[77] VEGF seems to be protective for motor neurons through a direct neurotrophic action,[76] but peripheral effects of VEGF are also likely. Activation of HIF-1, the master transcriptional regulator of the hypoxic response that binds to the hypoxia responsive element deleted in VEGFδ/δ mice, activates glycolysis and decreases mitochondrial respiration.[78] This action suggests that HIF-1 activation has similar effects to swimming. In human beings, the most compelling evidence for an impaired hypoxic response in ALS is the existence of mutations in the *ANG* gene. Although not frequent, these mutations can lead to ALS through genetic alteration of the hypoxic response, which supports the findings in VEGFδ/δ mice.[79] VEGF haplotypes might also confer a risk of developing ALS,[80] but this was not replicated in all ALS cohorts, which suggests a population-specific effect.[81]

Statins

Three epidemiological surveys have identified increased incidence of ALS in patients treated with statins,[82–84] but this relation has been challenged.[85] Moreover, statin intake has been associated with worsened outcome in patients with ALS.[86] The effect of statins on energy metabolism is a potential double-edged sword. They are likely to decrease LDL availability to skeletal muscle by inhibiting cholesterol synthesis, which could decrease or shut down the supply of nutrients to muscle in patients with ALS. Statins, however, also attenuate insulin resistance, which improves the supply of nutrients to muscle and helps to maintain neuromuscular health. Further experimental work is needed to delineate the beneficial effects, detrimental effects, or both, of statins on ALS.

Consequences for nutritional management

The importance of nutritional management in ALS has been stressed in the guidelines of the American Academy of Neurology[87] and the European Federation of Neurological Societies.[88] Initial management consists of dietary counselling, modification of consistency in the types of food eaten, and prescription of high-calorie supplements. No consensus has been reached on the timing of tube feeding, and decisions are currently based on presence of dysphagia, nutritional status, and respiratory function.[88,89] Percutaneous endoscopic gastrostomy is the standard procedure.[87,89,90] An alternative approach is percutaneous radiological gastrostomy, which has the advantage of not requiring sedation and is, therefore, recommended for patients with respiratory insufficiency, usually when forced vital capacity is more than 50% of that predicted.[87–90] Nasogastric tube placement is a minor procedure that can be beneficial for renutrition before gastrostomy placement, but is not a long-term solution owing to several side-effects, most notably an increase of oropharyngeal secretions along with nasopharyngeal discomfort, pain, and ulcerations.[89,91,92] Finally, home parenteral nutrition has been proposed as an alternative to enteral feeding in patients with advanced ALS and poor respiratory function, but has been assessed in only one single-centre observational study, and further studies are needed to clarify the efficacy and safety of this approach.[93]

Enteral nutrition probably enables stabilisation of bodyweight and prolongs survival, but definitive, evidence-based data are lacking.[87–90] A prospective, multicentre study has suggested that gastrostomy improves quality of life in patients with ALS.[94] Further well designed, controlled studies to assess the optimum time to start enteral nutrition and its effect on quality of life and survival in patients with ALS are urgently needed.

Two clinical trials to assess modification of the metabolic status of patients with ALS are currently underway, one evaluating a high-calorie versus a high-calorie and high-fat diet, received via percutaneous endoscopic gastrostomy or jejunostomy,[95] and one evaluating the use of olanzapine for weight gain in patients with ALS with more than 10% weight loss in the previous year (figure 2).[96] The first[95] is a randomised, placebo-controlled study to assess safety. The placebo group receive a balanced diet that provides 100% of daily energetic needs, a high-calorie (29% gained through fats) diet group receives 150% of daily energetic needs, and a high-calorie and high-fat diet group receives 150% of daily energetic needs with 55% of calories obtained through fats. The second[96] is a randomised, stratified, placebo-controlled, parallel-group trial investigating the efficacy and tolerability of 10 mg oral olanzapine in combination with riluzole. Both these clinical trials offer interesting perspectives and their results might have profound consequences for the clinical management of patients with ALS. A major pitfall of both these interventions, however, is that they might precipitate insulin resistance in patients with ALS, who could already be at risk of developing glucose intolerance at baseline.[27] The results of these

Search strategy and selection criteria

We searched Medline for articles published between January, 1960, and September, 2010, with the search terms "amyotrophic lateral sclerosis" and "motor neuron disease", in combination with "metabolism", "energy expenditure", "lipids", "diabetes", "mitochondria", "ApoE" or "cholesterol". Only full-text reports written in English or French were selected. We also used articles from our own files and databases when appropriate.

trials will undoubtedly provide at least partial answers as to whether targeting defective metabolism in ALS is an efficient way to alter disease progression. In the case of negative results, analysis of insulin and glucose levels in treated patients should retrospectively help to address whether trial failure was due to unsuccessful treatment or to increased insulin resistance.

Conclusions

Clinical and experimental studies have shown indisputably that abnormal energy homoeostasis has a role in ALS, and that therapeutic strategies should be aimed at correcting defective energy metabolism, but definitive data are scarce. Research in ALS should be directed by findings in other disorders. For instance, the incidence of diabetes is higher among patients with Huntington's disease[97] and Alzheimer's disease[98] than in the general population, and high-fat feeding in mouse models of the latter disorder exacerbates disease progress,[99] whereas caloric restriction is associated with a better outcome.[100] Animal models of Alzheimer's disease show development of mild insulin resistance, and those of Huntington's disease show prominent diabetes associated with severe defects in thermogenesis.[101] Lastly, most of the genes related to Parkinson's disease are involved in mitochondrial physiology.[102] Neurodegeneration is, therefore, often associated with and is potentially caused by defective energy metabolism. Future clinical and experimental studies, therefore, need to concentrate on the complex relations between energy metabolism and neurodegeneration, and should, at least in part, answer the question of whether targeting defective metabolism in ALS is an efficient way to alter disease progression. In terms of disease management, in addition to trials testing new therapeutic approaches, classic ALS nutritional therapies, such as percutaneous endoscopic gastrostomy, should be assessed further to clarify specific features of treatment, such as optimum timing, impact on quality of life and survival, and the biochemical nature of nutrients to be delivered. Research in new animal models and clinical cohorts into the molecular basis of ALS-linked hypermetabolism is also needed.

Contributors

All authors were involved in the writing and critical review of the article.

Conflicts of interest

ACL is a member of the scientific advisory board for Teva, Hoffmann-La Roche, and Lundbeck. LD, PFP, and JPL declare that they have no conflicts of interest.

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